ATTACHMENT 8

Expert Report on the Pharmaco-Toxicological (Pre-Clinical) Documentation of Humet-R Syrup

1999

Compiled by László Német DVM, PhD.

INTRODUCTION

HUMET-R SYRUP is a roborating product for macro- and microelement supplements.

Humic acids and 16 kinds of amino acids compose the carrier part of the product, which is enriched with essential macro and micro elements. Ten ml flavoured syrup contains total amount of 75 mg humic acid, 36 mg potassium, 15 mg magnesium, 14 mg iron, 10 mg zinc, 3 mg manganese, 0.5 mg vanadium, 0.2 mg cobalt, 0.17 mg molybdenum, and 0.13 mg sclenium. The recommended daily oral dose for adult is 10 ml syrup. Metals are bound through multiple chelate bonds to the polypeptides and phenol carbonic acids are connected to the fleteroaromatic nucleus.

Therapeutic indications are followings:

- -lt is a general roboration in convalescence periods.
- -For elderly people the product helps tracing element deficiency conditions.
- -Humet-R helps strengthening resistance of the organism and preventing diseases in epidemic periods.
- -lt improves mental and physical performance.
- -The product ceases iron deficiency.
- -It supplements iron in conditions with blood loss (e.g. in women's period Humet-R is on market since 1993. It has been approved by the Hungarian National Institute of Pharmacy and it has been registered under OGYI 430/1993 number in the OTC category. It is also registered in the following countries: Slovak Republic; Belarus, Russia, and Ukraine and is submitted for registration in Canada, Lithuania, and Yemen Republic.

TOXICITY

Single dose toxicity

Humet: Acute oral toxicity study in the rat

(See: attached Table of Contents of tabulated study reports and Tabulated Study Reports on Page:1)

According to the first non GLP single dose toxicity test in rats, no sign of toxicity and no death occurred even in the 10000 mg/kg treated group. It was estimated that the LD₅₀ dose of Humet is over 10 g/kg.

Usually drugs which cause no sign of toxicity or death in 2000-5000 mg/kg dose could be considered as no toxic. However, doses were calculated in case of this first non GLP toxicity to the whole amount of the finished product.

Acute oral toxicity of supplemented humic acid (DHS) in two species mice and rats (see:Tabulated study report Page:2-3)

Intrinsic safety profile of Humet R in single dose was more precisely demonstrated by acute oral toxicity "limit tests" using mices and rats. "Limit test" is usually used in case of non toxic substances. The test is designed for two groups: control and treated and treated group should have used the highest applicable dose. In case of Humet-R the highest dose was limited by the applicable highest volume (40 ml/kg). This was 4 times higher then in (non GLP) preliminary one at both species. No death or toxic symptoms occurred after the treatment and during the 14 days observation period. It was considered that the minimal toxic dose and LD₃₀ are above 40 ml/kg. Humet-R syrup which is equivalent of 600 mg/kg active ingredients content calculated for humic acid and also equivalent of 2292 mg/kg of dry matter of the product.

Repeated dose toxicity

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Effect of prolonged dose on rats

(See: Tabulated study report Page 4)

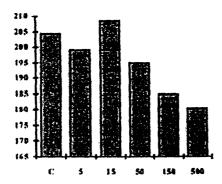
A 28 days non GLP study was conducted in order to clarify the possible side effects of Hurnet-R after repeated administration. To achieve a high and wide concentration range Hurnet-R was mixed into the normal rat food in a syrup free condition and rats were fed for 28 days in the following doses: 5, 15, 50, 150, 500 mg/kg. It was estimated that rats consume 20g food pro day. Ten female animals were used in the experimental groups. The control group was supplied by normal rat food.

Animals were observed daily, body weight was measured weekly, and parameters of clinical chemistry, hematology and organ weights were measured at the time of necropsy. Deviations from a regular type repeated dose toxicity study is the following: only one sex was used. Measuring of food consumption, water consumption, urinalysis and histological evaluation were not employed.

No death occurred during the treatment. Body weight gain decreased from the 3rd week in 150 and 500 mg/kg treated groups dose dependently. Body weight, kidney and liver

weights were significant lower in the same groups at the end of the study. No other change could be detected by hematology or clinical chemistry. It can be stated that NOEL and NOAL are over the oral 50 mg/kg dose in female rats.

In the following chart body mass changes are demonstrated after a 4-weeks feeding of syrup-free HUMET®-R on female rats (ten animals each per group, C = Control). Ordinate: Body mass group means in gram. Abscissa: syrup-free Humet-R humic dose in mg/kg. In 150 and 500 mg/kg treated groups body weight were decreased (P < 0.05) compared to the untreated control group.



Mutagenicity

Reverse mutation assay in Salmonella typhimurium

(see: Tabulated study report Page 5-9)

Investigating reverse mutation assay using Salmonella typhimurium tester strains assessed mutagenic potential of HUMET-R. Mutagenic activity was evaluated by measuring reversion of histidine auxotrophs to prototrophs.

Results of the study showed that Humet-R did not induce increases in the number of revertant colonies at any dose-level, in the five salmonella strains, either in the absence or presence of S9 metabolism. The test substance had no mutagenic activity and no bactericide effect under the reported experimental conditions. (\leq .7500 µg testsubstance /plate with preincubation)

According to the corresponding CPMP/ICH/141/95 guideline "Genotoxicity: Guidance on specific aspects of regulatory genotoxicity tests for pharmaceuticals"; the recommended highest concentration is 5000 µg testsubstance /plate.

Clastopenic and anticlastogenic effect

(see: Tabulated study report Page 10-11)

The clastogenic and/or the possible anticlastogenic properties of the Humet-R were reported in two in vitro mutgenicity tests on human lymphocytes. Even in much higher concentrations than the physiological dose Humet-R did not reveal chromosomal damage. The anticlastogenic effect was investigated in the second step using 200 rad x-ray to induce chromosomal aberration in human lymphocytes at much lower Humet concentrations (protective agent) in media. Although the number of di-centric ring aberrations decreased together with decreasing of Humet-R concentration, number of aberrant cells decreased only at one intermediate concentration of Humet. However, the result suggests certain condition in vitro anticlastogenic effect of Humet but this can not be considered as a proven fact.

PHARMACODYNAMICS

Effect of supplemented and un-supplemented humic acids on the metabolic balance in rats.

(see: Tabulated study report Page 12)

Three groups of female Wistar rats were tested. Two groups were gavaged daily by gastric tube with supplemented and un-supplemented humic acid for 31 days.

At the end of the experiment animals were killed. After extirpation of the stomach and intestine rest of the body was incinerated. The ash solutions were investigated with atomabsorption analysis. The whole body content of Ca, Mg, Mn, Cu, Za and Fe were determined. As a result of the above mentioned test, supplemented humic acid treatment increased the whole body contents in Fe, Ca, and Mg.

Effect on iron deficiency

(see: Tabulated study report Page 13-16)

Aim of the study was to determine the effectiveness of different formulations of macro and micro elements supplemented humic acids in the treatment of iron deficient rat pups. During the whole gestation and lactation period and thereafter up to the offspring's 21st day, normal control offspring and their mothers were fed with normal rat food while other dams and their offspring were fed with iron deficient diet (< 5 ppm). Six groups of iron deficient offspring were configured, five of them were treated with different formulation of supplemented humic acid. All formulas of the macro and micro elements supplemented humic acid proved to be effective in improvement of the general status and laboratory parameters in iron deficient animals. The effect was comparable to Aktiferrin. The best result was achieved by the Humet-R syrup treatment (Gr4.). Even the serum trigliceride level normalised in this group up to the end of the study, while it left low after the Aktiferrin treatment

Effect on systemic 25Sr and 103Ru pollution

(see: Tabulated study report Page 12)

Aim of the study was to investigate the effect of Humet-R treatment in systemic exposition of radioactive ⁴³Sr and ¹⁰³Ru salts. Animals were treated with radioactive ³³SrCl₂ in a 250 μg/kg (3.7 MBq/kg) oral or parenteral (i.p.) dose or ⁸⁵Sr was applied in humic acid complex, while ¹⁰³Ru salt (NH4)₂Ru[(H2O).Cl₅] was applied orally in 90.9 mg/kg (1.91 MBq/kg) dose aloae or in humic acid complex.

Conclusions:

Group 1-2: (Aim: determination of radioactivity in faces and urine after one p.o. dose of

**Sr salt and **Sr-humic acid complex)

The cumulative urinary excretion of ²⁵SrCl₂ treated animals at 96 hours: 2,87 ± 0,65. (% of dose).

The cumulative urinary excretion of ²⁵⁵ Humic a. complex treated animals at 96 hours: 1.59±0.42 (% of dose). Explanation: Less ²⁵Sr were absorbed from the complex than from the solution.

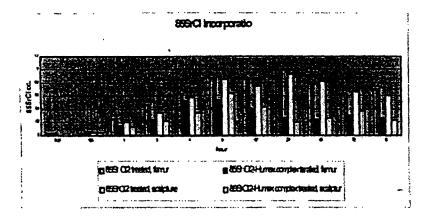
Less quantity of radioactivity was eliminated via the stool in the first 24 hours in animals treated with \$5Sr-Humic a complex. By the 96th luxurs, the difference between the two groups eliminated.

Group 3-5: (Aim: determination of radioactivity in faces and urine after one i.p. dose of ⁸⁵Sr salt and 24 hours thereafter one or four times repeated p.o. dose of ⁸⁵Sr-humic acid complex)

Oral administration of humic acid (once or repeatedly) did not influence the urinary and faccal excretion of ^{a5}Sr.

Group 6-7: (Aim: determination of radioactivity in tissues of 16 organs urine after one p.o. dose of \$3 Sr salt and \$5 Sr-humic acid complex at 12 times)

Significant less 85 Sr incorporated in to the bones at 85 Sr-Humic a. complex treated unimals than at 85 SrCl₂ solution treated ones after 96 hours of the threatment.



Group 8-9: (Aim: determination of radioactivity in faces and urin after one p.o. dose of 103Ru salt and 103Ru-humic acid complex)

There were no detectable differences in urinary and faecal excretion of ¹⁶³Ru between animal treated with the ¹⁶³Ru salt solution alone or with the ¹⁶³Ru -complex. Less amount of radioactivity was found in the tissues of animals treated with the complex preparation than in the control.

It is supposed that less 103Ru were absorbed from the complex than from the solution.

Cardioprotective effects

(see: Tabulated study report Page 19-20)

Cardiac failure and arrhytmias have particular role in mortality of patients suffering from ischemic heart disease. The most significant biochemical mechanism is generation of oxygen free radicals at the onset of reperfusion. This underlines the manifestation of ventricular fibrillation. It was supposed that selenium and humic acid may play a protective role with encouragement of antioxidant mechanisms.

The cardioprotective and antiarrhytmic effects were studied on isolated working rat heart after 2 weeks oral treatment with 30 mg/kg humic acid and 10 and 30 mg/kg Humet-R. Both humic acid and Humet-R showed some cardiprotective effects on ischemic myocardium, and no effect on nonischemic myocardium.

The most significant cardioprotective and strong antiarrhitmic effects were caused by the 2 weeks trentment with 10 mg/kg Humet-R. The mechanism can not be answered on the basis of this study but anti oxidant mechanism could be supposed.

Effects on the sexual activity

(see: Tabulated study report Page 21)

Research of compounds increasing sexual activity (aphrodisiacs) requires appropriate experimental models. Principle of the method developed by the author's team: an appropriately long 'deprivation' makes adult male rats chronically unable to display the complete sexual behavioural pattern (mounting, intermission, and ejaculation) even if a receptive female is present. During the weekly mating check-ups, such males behave either sexually inactively (show no copulatory pattern at all), became 'mounting-only', or they were 'sexually lazy' males who were incapable of intermission and/or ejaculation. If an aphrodisiac treatment is really efficient, male rats selected in this way will again display the complete mating behaviour in the presence of a receptive female. This method had allowed the discovery of the aphrodisiac effect of deprenyl, a world-wide known drug (Jumex, Movegan, Eldepryl) employed with success in Parkinson and Alzheimer's disease.

The other way employed by author was the selection of sexually inactive dotard (10-30 month old) male rats. Definition: sexual inactivity was confirmed at male rats who did not

show any reaction (mounting, intromission, ejaculation) at presence of recipient female one after other four challenges.

The effect of Humet-R and different solutions of Humet-S were studied on different aged adult and dotard sexually inactive male rats.

At the first experimental series 10 months old sexually inactive male rats were investigated. Eight animals were treated daily with Humet-R in a dose of 1 ml/animal for 15 weeks, as a contrast of 10 control animals were treated with 1 ml of 5% glucose. The treatment was followed by a 30 weeks post-treatment observation period. The sexual challenge was employed once a week for 30 minutes.

All Humet-R treated males become sexually active during the treatment period and full copulatory repertoire could be detected up to the end of post-treatment observation period. The sexual agility developed at eight males with the following latency:

1.3.4.4.1.1.13.17 weeks respectively. Two males become also sexually active in the control group but loosed their sexual ability during the post-treatment period.

Humet-S was investigated in a series of experiments employed different doses (0.1, 0.25, 1 ml animals) and different aged (10-30 month old) sexually inactive male rats. Results were similar to Humet-R. After a shorter latency period, one-third to half of the males recovered their sexual activity.

Even in case of three 30 months old dotard one recovered and displayed full scale of copulation after the fourteenth treatment. This result is quite surprising because a male rat looses his ejaculatory ability at age of 24 months.

CONCLUSIONS:

Considering all the pharmacological pattern and toxicological character achieved on laboratory tests and animals it is concluded that the oral administration of Humet-R in the recommended dosages will not produce any toxic effect.

From the pharmacological point of view Humet-R can be used according to the therapeutic indications and will become effective in strengthening conditions as roborant.

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TABULATED [Company: STUDY REPORT ON-MULTIPLAN Lid. ref.to ITLA.110 Finished Product: **IUMET-R SYRUP SYRUP** Page / Number Active Ingredient: 1/1 acid, Potassium, Magnesium, Iron, Zinc, sese, Copper, Vanadium, Cobalt, Molybdenum, **HUMET: ACUTE ORAL TOXICITY STUDY** E DOSE TOXICITY IN THE RAT Addendum No.: ent : HUM 001 Volume : Page: do Number: 2148/1/90/OETI Study period (years): 1990 : 6 November 1990 a/Strain : Rats, H-Wiston Number of animals : 84 Dose [mg/kg] : max. non lethal : 10000 nistration route : oral gavage by gastric tube min. lethal :>10000 Observation period : (Appl.day = Day 1) ment of controls: 15 days (5) 7400 (6) (3) (3) (4) (1) roup: 5500 10000 3000 4100 : 117 70 m m m 8 m 7 17 7 7 je. 0 0 ٥ 0 0 0 0 0 0 0 0 V. bours 0 0 0 0 0 a 0 0 0 0 7- hours 0 hay 2-7 0 0 0 O 0 0 0 0 0 0 0 0 0 0 0 0 0 my 8-end of observ. 0 0 0 0 0 Cotal nary of salient findings: product of Humet was used as test item, 18 hours starvation was employed before the treatment > 1-6; No toxic symptoms, no death, no treatment related finding at the autopsy conducted by the applicant: | | Yes |x|No o", indicate the name and address of the institute that conducted the study : NAL INSTITUTE OF FOOD AND NUTRITION SCIENCE Gyali in 3/a 1097 Budapest, Hungary, | | Yes | x | No Not required y in compliance with GLP: Page: 1

Name of Company: HORIZON-MULTIPLAN Ltd Name of Finished Product: HUMET-R SYRUP Name of Active Ingredient: Humic acid, Potassium, Magnesia Manganese, Copper, Vanadium, O Scienium REPEATED DOSE TOXICI	, denum, MET-R: Eff	lect	STUD ref. (Page 1	BULATED BY REPOR BY R			
Ref. to document: HUM 032 Report date: March 30 1994	Number:	Page: -		to-	-	ddendum i ried (years)	
Species/Strain: RAT, WISTAR	remales			T			\bigcirc
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Administration route: by food Treatment of controls: Group 1: Untreated, on normal fo				eight: 150	-170 g ini	study itiation	
Study group	nup control Humet-R 5 mg/kg				Humet- R 50 mg/kg	Humet-R 150 mg/kg	Hamet-R 500 mg/kg
Sex (m/f)	(m/f) f f					٢	ſ
Number of test animals	10	10	11	0	10	10	10
Number of animals died or sacrificed in extremis	0	0	0		0	0	0
Clinical observations: x yes no Clinical chemistry: x yes no Food consumption: yes x no Urinalysis: yes x no Urinalysis: yes x no Organ weights: x yes no Necropsy: x yes no Histology: yes x no							
Additional information: doses a	nd food consur	sption were	calc	ulated for 2	Og/animal/	day	
Conclusions: - Body weight p groups. Body kidney and liv the study.	er weight w	ere signific	nes	t lower i	n the same	groups at t	rested be end of
Histology performed accord	licant :				[] Yes	[x] No [x] No	
If "no", indicate the name a Dep. of Toxicology, Health It Study in compliance with G	istitute of H	of the insti ungarian Ai Yes	my	, 1456 B	udapest, Pf.	19., Hunga Not requir	ed
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TABULATED Name of Company: HORIZON-MULTIPLAN LIG STUDY REPORT Name of Finished Product: ref.to III.D.110 **HUMET-R SYRUP** Page / Number Name of Active Ingredient: 1/5 Humic acid, Potassium, Magnesium, Iron, Zinc, Manganese, Copper, Vanadium, Cobalt, Molybdenum, Selenium REVERSE MUTATION IN SALMONELLA MUTAGENIC POTENTIAL In vitro THYPHIMURIUM Ref. to document: HIJM 008 Volume: Addendum No.:-Page: -10 -Report date: 1 Oct. 1992 Number: 92/134-007M Study period (years): 1992 SALMONELLA THYPHIMURIUM TA 98 Test cells: hase substitution and frameshift point mutation Test for induction of: Aroclor 1254 induced rat liver S 9-mix Metabolizing system: a) solution: 468.75, 937.5, 1875, 3750, 7500 ng/plate Formulation of test substance b) solution: 468.75, 937.5, 1875, 3750, 7500 µg/plate and final concentration : a) 48 hours, no recovery time Treatment and b) 48 hours, no recovery time recovery time: a) 1% aqueous potassium-pyrophosphate Solvent and b) 1% aqueous potassium-pyrophosphate Final concentration : Pormulation of positive Control and final a) 4-nitro-o-phenilenediamine; 4 µg/plate b) 2-Aminoanthracene; 4 µg/plate Concentration Number of replicate cultures : Number of independent experiments: a) 2 (without metabolic activitation) a) 3 plates per concentration b) 3 plates per experiments b) 2 (with metabolic activitation) a) ---Number of cells analysed per culture: b) --Cytotoxic effects: a) ... Genotoxic effects: a) The test substances did not induce increases in the number of revertant colonies b) Similar to the control values at any dose-level, either in the absence or presence of \$9 metabolism Effects of the positive control: a) 2142 plate counts (exp.1) resp. 584 (exp.2); solvent control 34 (exp.1) resp. 34 (exp.2) b) 3221 plate counts (exp.1) resp. 384 (exp.2); solvent control 39 (exp.1) resp. 38 (exp.2) Additional data regarding methods and time schedule of the test: -Test item was the hophised form of the finisched productwith a 78.5 g/l of dry remnant content -To demonstrate mutagenic effect the concentration of \$9 fraction was increased up to 30 % and a 30 minutes preincubation time was established in the second study. Ix No Study conducted by the applicant: | | Yes If "no", indicate the name and address of the fastitute that conducted the study : Toxicological Research Centre Ltd. Szabadságpuszta Veszprém H-8200 Hungary EUROPE Not required | | No Study in compliance with GLP: |x| Yes Page: 5

TABULATED Name of Company: STUDY REPORT HORIZON-MULTIPLAN Ltd. Name of Finished Product : ref.to IILD.110 HUMET'-R SYRUP Name of Active Ingredient: Page / Number 2/5 Humic acid, Potassium, Magnesium, Iron, Zinc, Manganese, Copper, Vanadium, Cobalt, Molybdenum, Selenium REVERSE MUTATION IN SALMONELLA MUTAGENIC POTENTIAL In vitro THYPHIMURIUM Ref. to document : HUM 008 Volume : Addendum No. :---Page: -to ---Number: 92/134-007M Study period (years): 1992 Report date: 1 Oct. 1992 SALMONELLA THYPHIMURIUM TA 100 Test cells: base substitution and frameshift point mutation Test for induction of : Aroclor 1254 induced rat liver S 9-mix Metabolizing system: a) solution: 468.75, 937.5, 1875, 3750, 7500 µg/plate Formulation of test substance and final concentration : b) solution: 468.75, 937.5, 1875, 3750, 7500 µg/plate a) 48 hours, no recovery time Treatment and b) 48 hours, no recovery time recovery time: a) 1% aqueous potassium-pyrophosphate Solvent and b) 1% aqueous potassium-pyrophosphate Final concentration: Formulation of positive Control and final a) Methyl methane sulphonate: 2 µg/plate b) 2-Aminoanthracene; 4 µg/plate Concentration Number of replicate cultures: Number of independent experiments: a) 2 (without metabolic activitation) a) 3 plates per concentration h) 2 (with metabolic activitation) b) 3 plates per experiments Number of cells analysed per culture : b) ---Cytotoxic effects: a) --h) ---Genotoxic effects: a) The test substances did not induce increases in the number of revertant colonies b) Similar to the control values at any dose-level, either in the absence or presence of \$9 metabolism Effects of the positive control: a) 1454 plate counts (exp.1) resp. 1096 (exp.2); solvent control 133 (exp.1) resp. 141 (exp.2) h) 2028 plate counts (exp.1) resp. 799 (exp.2); solvent control 143 (exp.1) resp. 147 (exp.2) Additional data regarding methods and time schedule of the test : -Test item was the hyophised form of the finisched productwith a 78.5 g/l of dry remnant content To demonstrate mutagenic effect the concentration of S9 fraction was increased up to 30 % and a 30 minutes preincubation time was established in the second study. [a] No Study conducted by the applicant: [] Yes If "no", indicate the name and address of the institute that conducted the study; Toxicological Research Centre Ltd. Szabadságpuszta Veszprém H-8200 Hungary EUROPE | | Not required Study in compliance with GLP: [2] Yes | | No Page: 6

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ORIZON-MULTIPLAN Ltd.	ł	STUDY R		
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HUMET-R SYRUP			Į	
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ef. to document: HUM 004 Volume:	Page:		Addendum No.:	
Report date: 1992 Nun	nber:	St	udy period (years): 1992
Test cells: Peripheral !	human lymphoc	ytes		
Test for induction of : Anticlastog	genic effect			
Metabolizing system: Non				
Formulation of test substance	a) solut	ion: 1, 2, 5, 10 μl/1	ml culture	
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HUMET-R SYRUP Name of Active Ingredient:	Page/Number	
Humic acid. Potassium. Magnesium. Iron. Zinc.	1/1	1
Manganese, Copper, Vanadium, Cobalt, Molybdenum, Sclenium		
Manganese, Copper, Vanadium, Cobalt, Molybdenum,	The effect of supplemented and ur humic acids on the metabolic balan	
Manganese, Copper, Vanadium, Cobalt, Molybdenum, Selenium PHARMACODYNAMICS	The effect of supplemented and ur humic soids on the metabolic balan	ice in rats

Experimental design:

Three groups of female Wistar rats were tested. Two groups were gavaged daily by gastric tube with supplemented and unsupplemented humic acid for 31 days.

At the end of experiment animals were killed. After the extirpation of the stomach and intentines the rest of the body was incinerated. The ash solution s were investigated with atomabsorption analysis. The whole body content of Ca, Mg, Min, Cu, Zn and Fe were determined.

Results:

Ciroups	Ca	Mg	Mn	Cu	Zn	Fe
	(g/kg vet	(g/kg vet	(mg/kg vet	(mg/kg vet	(mg/kg vet	(mg/kg vet
	mass)	mass)	mass)	mass)	mass)	mass)
Control (No 8)	29,22	1,02	2,22	4,54	80,56	133,3
	± 3,05	± 0,06	± 0,21	± 0,94	± 2,5	± 6,75
Humic acid 320 µl/kg unsupplemented * (No 9)	26,48 ± 3,01	0.97 ± 0,05	2,11 ± 9,28	3,94 ± 0,58	79,03 ± 3,83	121,1 ± 10,8
l lumic soid 640 µl/kg supplemented * (No 9)	32,98 ± 4,03 4	1,1 ± 0,06 4	2,29 ± 0,2	4,99 ± 0,37	82,7 ± 5,33	148 ± 13,2 4

^{* =} The concentration of supplemented humic acid solution was the half of the unsupplemented ones

$\triangle = P < 0.05$ compared to the untreated control

Conclusions:

The unsupplemented humic acid treatment decreased the body contents in Fe, Ca, and Mg, while supplemented humic acid treatment increased the whole body contents in the same elements

Study conducted by the applicant:	Yes x	No	
If "no", indicate the name and address	s of the institute t	hat conducted the	itady:
Chemistry-Biochemistry, Pannon Univer EUROPE	rsity of Agriculture	d Science, 7400 Kaj	posvár Guba S. u. 40, Hungary.
Study in compliance with GLP:	Yes	[] No	x Not required Page: 12

		
Nume of Company:	TARULATED	
HORIZON-MULTIPLAN Ltd.	STUDY REPORT	
Name of Finished Product:	ref.to IILF.110	
HUMET-R SYRUP		
Name of Active Ingredient:	Page / Number	
Humic acid, Potassium, Magnesium, Iron, Zinc, Manganese, Copper, Vanadium, Cobalt, Molybdenum,	1 1/4	
Manganese, Copper, Vanadium, Cobait, Molyodenium,	1	
	Study on the effects of different form	ulations of
PHARMACODYNAMICS relating to proposed indication	humic acid bound with iron and other	
terring to bedoze more and	elements in iron deficient rat pups	
Ref. to document : 42-1-1 Volume : Page :	to - Addendum No. :-	
Report date: April 29, 1997 Number t	Study period (years) :	1997
Experimental design:		
Aim of the study was to determine the effectiveness of	of different formulations of macro and	d micro
elements supplemented humic acids in the treatment	of iron deficient rat pups. During the	whole
gestation and lactation period and thereafter up to the	offspring's 21st day, normal control	offspring
and their mothers were fed with normal rat food whill iron deficient diet (< 5 ppm) Six group of iron defici	e other dams and their ottspring were	ted with
trent delicient diet (< 5 ppm) Six group of iron delicitiented but treated with different formulation of supplemented but	mic acid, as follows:	incin were
Experimental groups:		ĺ
GR1. Normal control on normal diet		40 animals
Gr2. Iron deficient negative control on iron deficient (ID)) diet	40 animals
Gr3. Aktiferrin treated (3.7 mg/Fe/kg) positive control or	ı ID diet	40 animals
Gr4. HUMET-R Syrup suspension (3.7 mg Fe/kg, humic		40 animals
Gr5. Granulated I. HUMET specimen (3.7 mg Fe/kg, hun	nic a. 176 mg/kg), animals on ID diet	40 animals
Gr6. Granulated 11. HUMET specimen (3.7 mg Fe/kg, hu	mic a. 938 mg/kg), nnimals on ID diet	40 animals
Gr7. Dried HUMET specimen (3.7 mg Fe/kg, humic a. i	12 mg/kg), animals on ID diet	40 animals
	**	
Measured parameters:		
Weekly (dams and pups); body weight, relative body we	ight gain, food consumption.	
Once: fitter size, perinatal index, survival index		
On days 0, 7, 14, 21: Hematological and serum chemical MCH. MCHC, ZP (Zinc-protoporfirin/hem ratio), Se Fe (GPT), triglicerides	i parameters: RBC, WBC, Plateicts, Hb, , TIBC (total iron binding capacity), AS	HT, MCV. T (GOT). AL
Hemark: 0 day means the day of weaning		
Study conducted by the applicant: Yes	[1] No	
If "no", indicate the name and address of the institu		
National Occupational Health Institute, 1094 Budapest	Nagyvárad tér 2, Hungary, EUROPE	
Study in compliance with GLP: [] Yes	No	t required
		Page: 13

Name of Company:		TA	BULATED	
HORIZON-MULTIPLAN	Lid.	DY REPORT		
Name of Finished Produc		ref.to III.F.110		
HUMET-R SYRUP		<u> </u>		
Name of Active Ingredies	nt:	Pa	ge / Number	
Humic acid, l'otassium, M Manganese, Copper, Vana Sclenium	agnesium, Iron, Zinc, dium, Cobalt, Molybdenum,		2/4	
PHARMACODYNAMIC relating to proposed indica	CS ation	humic acid	e effects of differer bound with iron an iron deficient rat p	d other micro
Ref. to document : 42-1-1	Volume: Page: -	- to	Addendum l	ia. ;
Report date : April 29 19	97 Number:		Study period (years): 1997
he most important detai	ls of the results: Offspring's	body weight (g, means only)	
Days	0	7	14	21
	(n)	(a)	(a)	(n)
Grt. Normal control	7000	66,26 (40)	112.03 (33)	154.71 (17)
Gr2. Iron deficient		32.05	50.71	45.29
regative control	, · - /	(40)	(32)	(16)
ir3. Aktiferrin positive control		31.53 (35)	78.83 (25)	112.14 (15)
Gr4.		37.74 (35)	71.9 (25)	(04.33 (15)
GR3	22.89 (40)	36.97 (33)	66.12 (22)	101.89 (12)
Gr6.	21.46 (40)	37.5 (34)	70.33 (22)	113.58
Gr7.		36.59 (35)	69.42 (23)	105.7
* - P < 0.05 compared to the				
National Occupational	ame and address of the lasti Health Institute, 1094 Budapes	i Nagyvárad tér	2 Hungary, EUP	OPE
Study in compliance wi	ih GLP: []Yo	s N		Page: 14

Study on the effects of different formulations of humic acid bound with iron and other micro elements in iron deficient rat pups To - Addendum No.:-	Vame	of Company :	·····				TABULA	TED		······································
Page / Number 3 / 4 Study on the effects of different formulations of humic acid bound with iron and other micro elements in iron deficient rat pups ge: — to — Addendum No. :— Study period (years): 1997 (g/100 ml, resums Se Fe (µmol/t, means only) TIBC (µmol/t, means only) (n)	IORI	ZON-MULTIPL	AN Esci.			S	TUDY RI	EPORT	1	
Study on the effects of different formulations of humic acid bound with iron and other micro elements in iron deficient rat pups Study period (years) : 1997		of Finished Pro								
Study on the effects of different formulations of humic acid bound with iron and other micro elements in iron deficient rat pups Study period (years) : 1997	HUMET-R SYRUP								l	
Study on the effects of different formulations of humic acid bound with iron and other micro elements in iron deficient rat pups Study period (years) : 1997	Vario	of Active Ingree				1	Page / Ni	ımber		
Study on the effects of different formulations of humic acid bound with iron and other micro elements in iron deficient rat pups The study period (years) : 1997		e acid, Potassium		n Iron Zir	nc.					
humic acid bound with iron and other micro elements in iron deficient rat pups ge : — to — Addendum No. :— Study period (years) : 1997 (g/100 ml, means Se Fe (µisol/l, means only)	Mang Selen	anese, Copper, V	nadium, C	obali, Moly	hdenum,					
Study period (years) : 1997 (g/100 ml, means by) Se Fe (μinol/l, means only) (m)		RMACODYNAM				humic sc	id bound	with iron a	nd other mi	
Study period (years) : 1997		document : 42-1			Page: -	. I		· · · · · · · · · · · · · · · · · · ·	·····	
		rt date : April 29		Number			Sto	dy period (years): 19	97
(a) (a) (b) (c) (c) (c) (d) (d) (d) (d) (e) (e) (e) (e) (e) (e) (e) (e) (e) (e			RBC (TA,	means	Hb (g/10)	mi, mesas				oli, means
(a) (n) (n) (n) (n) (n) (n) (n) (n) (n) (n	ays	Groeps	8 (0)	21 (a)	(n)	,				
(12) 12.43 ** (15) 12.54 ** (15) 12.08 ** (n) (12) 187.70 4		Grl. Normal control	4,52 (7)	5.57 (12)	9.53 (a)	}				
(15) 12.54 ** (15) 46.5 ** 46.5 ** (15) 187.70 4		Gr2. Iron deficient negative control		6,04 (12)		1 ' -		1		
3.72 44 12.08 ** (n) 12.08 ** (12) 11.23 * 4 (12) 11.92 ** (12) 70.78 ** (13) 90.00 **4		Gr3. Aktiferrin positive control	1	5.46 * (15)	1	1				
12.08 **		Grt.		5.24 ** (15)	1			**		
(n)			2.57		3.72		6.52		187.70	
(12) (12) (12) (12) (12) (12) (12) (12)		GrS.	(6)	5.63 (12)		44			1 .	
AA (13) **A		GR6		5.54 (12)			1	1		***
4.4 (13)			4		4	11000	4	70.78 18	4	
		Gr/.		(13)		**				***
	** = 1 4 - 1		the iron def	5.54 (12) 5.55 (13) sicient control	(n)	(12) 11.23 * 4 (12) 11.92 **	(n)	(12) 68.99 ** (12) 70.78 **	(11)	9
	11"	dy conducted by no". Indicate the	name and	address o	Yes (the instit	use that con	ducted il	se study :	SUPE.	
x No lastitute that conducted the study : dapest Nagyvárad tér 2 Hungary. EUROPE		jonal Occupation y in compliance			Budapesi		No No	mgary. cui	[x] Not r	equired

NI	C				TABULATED	-
	e of Company:					
	IZON-MULTIPL				TUDY REPORT	}
Nami	e of Flaished Pro- HUMET-R SYR				Telico Mil.P. 110	
					Page / Number	1
	e of Active Ingre)		A/A	1
Mang Selen	ganese, Copper, Vi	. Magnesium. Iron. 2 anadium. Cobalt. Mo	hybdenum.			
	RMACODYNAN			humic ac	the effects of different forried bound with iron and other in iron deficient rat pups	
Ref. to	document : 42-1	-11 Volume:	Page:	to		
Repo	ort date : April 29	1997 Namb	er :		Study period (years)	: 1997
		AST (GOT) U/l. means on aly	Trigliceride. (mmoi / l. m			
Days	Groops	21 (u)	2 (n			
	Gr). Normal control	100.58 (12)	1.1 (n			
	Gr2. Iron deficient negative control	233.27 (12)	0.4	18 2)		
	Gr3. Aktiferrin positive control	146.58** **	0.58	A A 5)		
	Gr4.	160.36** 4 4 (15)		5)	:	
	Grs.	152.2** 4.4 (12)	1	4 * 2)		
	GR6	162.75°4	1	44 2)		
	Gr7.	153.92** 4 4		3)	-	

^{* -} P < 0.03 compared to the iron deficient control

Conclusions:

All formulas of the macro and micro elements supplemented humic acid proved to be effective in improvement the general status and laboratory parameters in fron deficient animals. The effect was comparable to Aktiferrin. The best result was achieved by the HUMET-R Syrup treatment (Gr4.). Even the serum trigliceride level normalised in this group up to the end of the study, while it left low after the Aktiferrin treatment.

Study conducted by the applicant :	[[Yes [x]		
If "ao", indicate the name and addres			
National Occupational Health Institute.	1094 Budapest Nag	yvárad tér 2 Hur	gary, EUROPE
Study in compliance with GLP:	[] Yes] No	x Not required

^{** =} p < 0.01 compared to the iron deficient control

A = P < 0.05 compared to the untrested control

TABULATED Name of Company: HORIZON-MULTIPLAN Ltd. STUDY REPORT Name of Finished Product: ref.to III.P.110 **HUMET-R SYRUP** Page / Number Name of Active Ingredient: 1/2 Humic acid, Potassium, Magnesium, Iron, Zinc. Manganese, Copper, Vanadium, Cobalt, Molybdenum, Report on the pharmacocinetic studies of **Sr- and **Ru-humic acid complex in rats PHARMACODYNAMICS in vivo relating to proposed indication Addendum No.:--Ref. to document: HUM 015 Volume: Page: --to -Number: Study period (years): 1993 Report date: Marc 30.1993 Experimental designe: Dose Route No Measuring Subjects Dose Treatment of points (hours) frequency FM 24, 48, 72, 96 Metabolic balance SrCl, sol. p.o. 3.3 1. 250 µ/kg (radioactivity in faces and urine) SrCl₂-24, 48, 72, 96 Metabolic belance p.o. 250 µ/kg 150 2. (radioactivity in faces and Humic acid mg/kg urine) complex 24, 48, 72, 96 | Metabolic balance 5-5 "SrCl, sol. 250 µ/kg i.p. (radioactivity in faces and urine) "SrCl, sol. 24, 48, 72, 96 Metabolic balance 250 µ/kg 150 i.p, 4.) (after (radioactivity in faces and Humic acid mg/kg p.o. urine) Metabolic balance 24, 48, 72, 96 SrCl₂ sol. 250 µ/kg 150 (radioactivity in faces and 4 (in every Humic soid p.o. mg/kg eripe) 24 h l 0.25, 0.5, 1. Radioactivity in tissues of 16 p.o. SrCl₂ sol. 250 μ/kg 2, 4, 8, 12, 24, 48, 72, 96 organs (3 animals/point) Radioactivity in tissues of 16 33 "SrCl_Humic 250 µ/kg 150 p.o. 0.25, 0.5, 1, 2, 4, 8, 12, acid complex. mg/kg 24, 48, 72, 96 (3 animals/point) 24, 48, 72, 96 Metabolic balance Ru sol. 90.9 mg/kg p.o. (radioactivity in faces and urine and organs (96h) 24, 48, 72, 96 Metabolic balance 5-5 Ru- Humic 90.9 mg/kg (radioactivity is faces and urine 320mg/kg acid complex and organs (96h)) Study conducted by the applicant: | | Yes [I] No If "no", indicate the name and address of the institute that conducted the study : Central Isotope Laboratory, Semmeliveis University of Medicine, Nagyvárad tér 4., H-1089 Budapest, Fungary, EUROPE | x | Not required | |Yes | | No Study in compliance with GLP: Page: 17

Name of Company:

HORIZON-MULTIPLAN Ltd. Name of Finished Product:

HUMET-R SYRUP

Name of Active Ingredient :

Humic acid, Potassium, Magnesium, Iron, Zinc, Manganese, Copper, Vanadium, Cobalt, Molybdenum, Selenium

TABULATED STUDY REPORT ref.to III.F.110

Page / Number 2/ 2

PHARMACODYNAMICS in vivo relating to proposed indication

Report on the pharmacocinetic studies of 15Sr- and Ru-humic acid complex in rats

Ref. to document: HUM 015 Volume: Report date: Marc 30.1993

Page : -Number:

Addendum No.:--

Study period (years): 1993

Conclusions

Group 1-2:

The cumulative urinary excretion of \$5SrCl2 treated animals at 96 hours: 2.87 ± 0.65 (% of dose)

The cumulative urinary exerction of ¹⁴Sr-Humic a. complex treated animals at 96 hours: 1,59±0,42 (% of dose). Explanation: Less amount of 45 Sr was absorbed from the complex than from the solution.

Less quantity of radioactivity was climinated via the stool in the first 24 hours in animals treated with *5Sr-Humic a. complex. By 96 hours the difference between the two groups eliminated.

The oral administration of humic acid (once or repeatedly) did not influence the urinary and faecal excretion of 45 Sr.

Group 6-7:

Significant less 83 Sr incorporated in to the bones at 83 Sr-Humic a. complex treated animals than the 83 SrCl₂ solution treated ones.

Group 8-9:

There were no detectable difference in urinary and faecal excretion of ¹⁰³Ru between the animals treated with the ¹⁰³Ru salt solution alone or with the ¹⁰³Ru -complex.

Less amount of radioactivity was found in the tissues of animals treated with the complex preparation, than in the control

Study conducted by the applicant: | | Yes | [x] No | If "no", indicate the name and address of the institute that conducted the study:

Central Isotope Laboratory, Semmelweis University of Medicine, Nagyvárad tér 4., 11-1089 Budapest. Hungary, EUROPE

Study in compliance with GLP:

| | Yes

[| No

|x | Not required

Page : 18

Name of Company:

HORIZON-MULTIPLAN Ltd. Name of Finished Product:

HUMET-R SYRUP

Name of Active Ingredient:

Humic neid, Potassium, Magnesium, Iran, Zinc, Manganese, Copper, Vanadium, Cobalt, Molybdenum, Selenium

ref.to 111.F.110 Page / Number 1/2

TABULATED

STUDY REPORT

PHARMACODYNAMICS relating to proposed indication Cardioprotective effects of SHA and HA preparations in the isolated working rat heart subjected to ischemia/reperfusion.

Ref. to document : HUM 39-1-08 Volume : Page : --Report date: June 3 1997 Number:

Addendum No. :---Study period (years): 1997

Experimental design:

Group 1. vehicle control

No 8 25 min. ischemia + 10 min. reperfusion

Circup 2. SIIA treatment 10 mg/kg for 2 weeks No 8 25 min. ischemia + 10 min. reperfusion

Group 3. SHA treatment 30 mg/kg for 2 weeks No 8 25 min. ischemia + 10 min. reperfusion

Group 4. HA treatment 30 mg/kg for 2 weeks No 8 25 min. ischemia + 10 min. reperfusion

SHA: macro and elements supplemented humic acid

HA: humic acid

Conclusions:

- 1. HA and SHA have no effect on the nonischemic myocardium
- 2. IIA has some beneficial effect on myocardial perfusion after ischemia and slight improves myocardial function.
- 3. SHA 10 mg/kg shows moderate cardioprotective and strong antiarrhitmic effect in the rat heart.
- 4. SHA 30 mg/kg although results in a tendency of cardioprotection and antiarrhytmic effect but the dose seems to be to high for 2 weeks treatment

|x| No Study conducted by the applicant: | | Yes

If "no", indicate the name and address of the institute that conducted the study :

Dep. Biochemistry, Biological Research Centre, 6726 Szczed Temesvári Krt. 62., Hungary, EUROPE

Study in compliance with GLP:

| x | Not required Page: 19

TABULATED Name of Company: STUDY REPORT HORIZON-MULTIPLAN LIJ. relio IR.F.110 Nume of Finished Product: **HUMET-R SYRUP** Name of Active Ingredient: Page / Number 1/2 Humic acid, Potassium, Magnesium, Iron, Zinc, Manganese, Copper, Vanadium, Cobak, Molybdenum, Selenium Cardioprotective effects of SHA and HA **PHARMACODYNAMICS** preparations in the isolated working rut heart relating to proposed indication subjected to ischemia/reperfusion. Ref. to document: HUM 39-1-08 Volume: Page: to ---Addendum No.:--Study period (years): 1997 Number: Report date: June 3 1997 Resultes: CF (ml/min) AF (ml/min) LVDP (kPa) HR (bom) Group No Before After Before Before After Before After ischemia ischemia ischemia ischemia ischemia ischemia ischemia ischemia Control 265±6 260±9.9 22,9±0,9 20.4±0.9 43.4±1.5 13.3±2.5 19.2±0.7 14.0±0.5 15.4±2.3 SHA 10 × 264±7 257±6 24.4±0.8 24.3±0.9 43.9±1.7 19.3±0.5 14.8±0.7 mg/kg 24.5±2.8 19.1±0.4 15.9±0.8 30 8 270±4 263±3 23,4±0.9 24.5±0.8 44.5±1.4 SHA mg/kg 19.0±0.6 15,3±0,7 30 257±5 23.0±0.9 23.7±0.9 44.9±1.6 19.1±3.6 HA 8 263±7 mg/kg VF (%) +dP/dt (kPa/s) -dP/dtmn (kPa/s) LVEDP (kPa) Group Affer Before After Before After Before Before After ischemia ischemia ischemia ischemia ischemia ischemia ischemia ischemia 304±20 0.51±0.04 1,53±0.09 87.5 10265±45 Control 609±53 463±33 1.35±0.07 62.5 SHA 10 1058±43 675±35 470±26 339±23 0.54±0.05 mg/kg 0.56±0.05 \$0.0±80.1 12.5 351±20 SHA 983±41 788±36* 451±20 30 8 mg/kg 37.5 0.49±0.04 1,25±0.08 HA 30 1044±45 708±44 445±21 340±14 mg/kg Abbreviations: HR (bpm): heart rate, CF (ml/min) coronary flow, AF (ml/min) aortic flow, LVDP (kPa) lest ventricular developed pressure, +dP/dtmax(kPa/s) and -dP/dtmin (kPa/s) maximum and minimum of first derivate of left ventricular pressure, LVEDP (kPa) left ventricular end-diastolic pressure, VF (%) ventricular fibrillation, *(p<0,05) |x| No Study conducted by the applicant: | | Yes If "no", indicate the name and address of the institute that conducted the study : Dep. Biochemistry, Biological Research Centre, 6726 Szeged Temesvári Krt. 62., Hungary, EUROPE | x | Not required Study in compliance with GLP: | | Yes | | No Page : 20

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Name of Company:

I KORIZON-MULTIPLAN Lid.
Name of Finished Product:

HUMET-R SYRUP

Name of Active Ingredient :

Humic acid, Potassium, Magnesium, Iron, Zinc, Manganese, Copper, Vanadium, Cobalt, Molybdenum,

Selenium

PHARMACODYNAMICS in vivo

TABULATED STUDY REPORT ref.to III.F.110

Page / Number 1/1

OBSERVATION OF THE EFFECTS OF HUMET DERIVATES ON MALE RAT'S SEXUALLITY

Ref. to document : HUM 013 Volume :

Report date: November1994 Number:

Page: -

- Addendum No. :--Study period (years) : 1994

Sexual inactivity can be reached by long term 'deprivation' which makes adult male rats chronically unable to display the complete sexual behavioural pattern (mounting, intromission, ejaculation) even if a receptive female is present:

After the above mentioned deprivation sexually inactive males were selected for HUMET-R Syrup treatment.

Sexual inactivity was confirmed at male rats who did not show any reaction (mounting, intromission, ejaculation) in the presence of recipient female one after the other four challenges.

Frequency of challenges: once a week for 30 minutes

Results:

Groups	Number of males	select	eeks ion peri	iod	i-15 w	eek ent peri	od				Latency in responded males
	responded/ tested	Mountings	Intromission	Ejaculations	Mountings	Intromission	Ejaculations	Mountings	Intromission	Ejaculations	wocks
5% glucose control I ml / day	2/10	0	0	0	83	34	7	0	0	0 -	3,4 resp.
HUMET-R Syrup 1 ml / day	8/8	0	0	0	408	253	19	237	133	21	1,3,4,4,4,11,13,17 resp.

Conclusions HUMET-R Syrap was found highly efficient in recovering sexual activity. The recovered activity was kept long after the last treatment

Study conducted by the applicant: [| Yes [x] No

If "no", indicate the name and address of the institute that conducted the study :

Pharm Expert Association, Pharmaceutical Institute, Semmelweis University of Medicine, Nagyvárad tér 4., 14-1089 Budapest, Hungary, EUROPE

Study in compliance with GLP:

1 IYes

1 | No

| 1 | Not required

Page: 21

CURRICULUM VITAE

Name:

Dr László Német

Date of Birth:

2nd February 1951

Place of Birth:

Budapest, Hungary

Family:

married

Professional Experience:

Pharmacological Research Institute for Drug Research 1974-80 1974-75 Associate Research Fellow 1975-80 Head of Dog Toxicology Plant at Dunakeszi

Chemical Works of Gedeon Richter Ltd., 1980-1997

1980-88 Toxicological Laboratory

Toxico-pathologist

1988-95 Pathological Laboratory

Pathologist and head of the laboratory

1995-97 Preclinical Development, Director of Dug Safety Laboratories: General Toxicology, Reproductive Toxicology, Pathology,

Pharmaco-Kinetics

State Control Institute for Veterinary Biologicals, Drugs and Feeds

1997- Pharmacological Department

Official in charge of approval of veterinary medical products

Education: 1969-74 University of Veterinary Science, Budapest.

Graduation: Doctor of Veterinary Medicine 1974

Postgraduate Courses:

1978-80 Training in Toxicology, Pustgraduate School of Veterinary Science, Budapest. Graduation: Veterinary Toxicologist 1980

One month fellowship in immuno-histochemie at the Pathological Institute of Veterinary University of Vienna, 1983

Training in Human Pathology Postgraduate School of Medicine, Budapest, 1987-88 One month fellowship in Frauenhofer Institut für Toxikologie und Aerosolforschung, Hannover, 1990

Histopathology Seminar on the Musculoskeletal System of Laboratory Animals, Hannover September 4-6 1990

Histopathology Seminar on the Special Senses of Laboratory Animals, Hannover September 4-6 1991

BSTP Training Course in Toxicological Pathology Pathology of the liver, Cambridge March 1994

IUPHAR Workshop on Biological Monitoring of Chemical Exposure, New Delhi Dec. 1997

Professional Societies:

Hungarian Society of Pathologists Union of Hungarian Toxicologists Hungarian Association of Laboratory Animal Sciences

Language : German, English

PC Skills: Excel, Win-Word, PowerPoint, Statistica

Number of presentations and publications: 24

Consulting lectures: 14

Budapest, 28th January, 1999

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Consulting Lectures

A szem toxikológiája (Toxikology of Eyes) OTE posztgraduális toxikológus képzés (Postgraduate School of Medicine, Seminar for Toxicologists), Budapest, 1984

A krónikus toxikológiai vizsgálat
(The Chronic Toxicological Study)
OTE posztgraduális toxikológus képzés
(Postgraduate School of Medicine, Seminar for
Toxicologists), Budapest, 1984

Good Laboratory Practice a gyógyszerbiztonsági vizsgálatokban. (The GLP in the safety studies.)
Szabvány műveleti eljárások készítése,
használata, karbantartása.
(Creating, using and maintaining SOPs.)
Budapesti Műszaki Egyetem Mérnőktovábbképző
Intézet. (Engineering Postgraduate Training
Institute) Budapest, 1991

Good Laboratory Practice a gyógyszerbiztonsági vizsgálatokban. (The GLP in the safety studies.)
A patológiai laboratórium és az archivum szervezése. (How to organize the pathological laboratory and archive.)
Budapesti Műszaki Egyetem Mérnőktovábbképző Intézet (Engineering Postgraduate Training Institute.)
Budapest, 1991

Gyögyszerész szakvizsga előkészítő.
(Training course for pharmacists.)
A patológia szerepe a gyógyszerbiztonsági vizsgálatokban.
(The role of pathology in safety studies.)
OGYI / National Institute of Pharmacy.
Budapest, from 1991 annually up to 1997

Az Európa Tanács állásfoglalása a kísérleti állatok védelméről (European Convention for the Protection of vertebrate animals......)

OTE Experimentális Toxikológia, posztgraduális képzés (Postgraduate School of Medicine, Experimental Toxicology), Budapest, 1991

Laboráliatok tartása, kezelése (Animal care, résearch) OTE Experimentális Toxikológia, posztgraduális képzés (Postgraduate School of Medicine, Experimental Toxicology), Budapest, 1991 Állattenyésztés, állathigiénia (Animal breeding, animal hygiene) OTE Experimentális Toxikológia, posztgradzális képzés (Postgraduate School of Medicine, Experimental Toxicology), Budapest, 1991

Laboráliattáp (Animal diets) OTE Experimentális Toxikológia, posztgraduális képzés (Postgraduate School of Medicine, Experimental Toxicology), Budapest, 1991

Laboratóriumi állatok fertőző betegségei (Infectious diseases of laboratory animals)
OTE Experimentális Toxikológia, posztgraduális képzés
(Postgraduate School of Medicine, Experimental Toxicology), Budapest, 1991

Laboratóriumi állatok higiéniai állapotának minősítése és betegségeik (necreditation of animal health status and diseases of laboratory animals)
ÁOTE szakosított továbbképző tanfolyam (Postgraduate Course of Veterinary University)
Budapest, from 1992 annually

A patológia szerepe a preklinikai gyógyszerbiztonsági vizsgálatokban (The role of Pathology in preclinical safety development)

DOTE kliniko-farmakológus tanfolyam
(Postgraduste School of Medicine, Clinical-Pharmacological Course)

Debrecen, 1995

Rágcsálók és nyúlajktak anatómiai jellegzetességei
(Anatomical caracteristics of rodents and lagomorphs)
A patológia alapfogalmai
(Basic concepts in pathology)
Laboratóriumi állatok fertőzőbetegségei
(Infectious diseases of laboratory animals)
Posztgraduális toxikológus képzés négy szemeszterben (Postgraduate Lectures in Toxicology),
Állatorvostudományi Egyetem Továbbképzési központ (Postgraduate School of Veterinary University), Budapest. 1997

A toxiko-patológiai laboratórium GLP szervezése.

(The GLP organisation in the toxico-pathological laboratory.)
Felfüggesztett gyógyszerfejlesztések kóroktani szempontból. Eset tanulmányok.
(Suspended drug developments from general pathological aspects. Case studies.)
Posztgraduális toxikológus képzés négy szemeszterben (Postgraduate Lectures in Toxicology),
Állatorvostudományi Egyetem Továbbképzési központ (Postgraduate School of Veterinary University), Budapest. 1998

Budapest, 28th January, 1999

habut Line

Addendum to the "Expert Report on the Pharmaco-Toxicological (Pre-Clinical) Documentation of Humet-R Syrup (1999)

2000

Compiled by László Német DVM, PhD.

Introduction

Because of the increasing demand of the market and with the development of manufacturing technology, two solid forms (HUMET Turbo Capsule and Humetta Effervescent Tablet) were developed of the original liquid HUMET-R Syrup.

The recommended daily oral dose for adults is 10 ml of HUMET-R Syrup which is equivalent with 75 mg humic acid (about 1 mg/kg human daily dose). The new solid products contain 1/3 of the liquid syrup which is equivalent with 25 mg humic acid pro capsule or tablet.

An additional toxicological study was conducted by feeding the active ingredient (potassium humate) in solid (powder) form with rats for 60 days, to prove the similarity of the toxicological profile of liquid and solid forms in repeated doses.

60-Day Toxicological Study of a Powder Humic Acid Product in Rats

(See: Tabulated study report Page 1, Addendum 1)

In the 60-day non GLP repeated dose study, the active ingredient; potassium humate was mixed in powder form to normal rat food in order to achieve a daily 60 and 240 mg/kg intake which is corresponds to 60 and 240-fold of the human dose The food consumption was calculated for an average of 20g food / animal / day. The control group was supplied by normal rat food. Only female animals were used, 16 in the control group and 20-20 in potassium humate fed groups.

According to the protocol five-five animals were sacrificed from each group on weak 2, 4, 6 and 8.

Animals were observed daily, body weight was measured weekly, and parameters of hematology and organ weights were measured at the time of necropsy.

Deviations from a regular type repeated dose toxicity study is the following: Study design, only one sex was used. Measuring of food consumption, water consumption, of clinical chemistry urinalysis and histological evaluation were not employed.

No death occurred during the treatment. Body weight decreased slightly from the 4rd week of treatment up to the end of study in the 60 mg/kg treated group, while the mean body weight remain comparable to the control in the 240 mg/kg group. No other significant changes occurred in the parameters of hematology or organ weights.

In the previous 28-day repeated dose study of HUMET-R Syrup in rats NOEL and NOAEL were estimated over the oral 50 mg/kg dose, based on the lowered body weights in female rats.

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Name of Company:		TABULATED					
HORIZON-MULTIPLAN Ltd				STUDY	REPO	RT	
Name of Finished Products:					III.B.1		
HUMET-Turbo Caps. and I	HUMETTA T	Tabl.					
Name of Active Ingredient:				Page / Number			
Potassium humate			1/1				
REPEATED DOSE TOXICI		Day Toxico luct in Rats		cal Study	of a Pov	vder Hum	ic Acid
Ref. to document: HUM 057 Report date: March 30 1994		Page:		to			ım No.: - ars): 1998
Species/Strain: RAT, WISTAR I	emales			٠			
Number of animals: 56				Duratio	n of trea	tment: 6	0 days
Observation period after the en	d of dosing:	0					
Administration route: by food						***************************************	
Treatment of controls: Group 1: Untreated, on normal for	od			Age : Body wei	ght: 1'	70-190 g	at study initiation
			-	Treatme	nt days p	per week :	7
Study group	control	Humet- powder 60 mg/kg	po	met wder 0 mg/kg			
Sex (m/f)	f	f	f				
Number of test animals	16	20	20				
Number of animals died	0	0	0				
Or sacrificed in extremis							
Clinical observations: [x] yes Food consumption: [] yes Water consumption: [] yes Body weight: [x] yes Hematology: [x] yes	s [x] s [x] s []n	no no	Uri Org Nec	nical chem nalysis : gan weigh cropsy : tology :	ts:	[] yes [] yes [x] yes [x] yes [] yes	[x] no [x] no [] no [] no [x] no
Additional information: Doses w Five-five animals were sacrificed					onsumptio	on / animal /	day
Conclusions: - Body weight d treated group.	ecreased fro	om the 4 th	weel	k up to th	e end o		
Histology performed according Study conducted by the apple	icant :]] Yes] Yes	[x] [x]	Vo
If "no", indicate the name as Dep. of Toxicology, Health In	stitute of Hu	ıngarian A	rmy,	1456 Bud	lapest, F	Pf. 19., Hu	ngary, Euro
Study in compliance with Gl	LP:	[] Yes	[x] No	•] Not req age : Add	

Name of Company:	TABULATED
HORIZON-MULTIPLAN LID	STUDY REPORT
Name of Finished Product:	ref.to III.D, 110
HUMET-R SYRUP	
Name of Active Ingredient:	Page / Number
Humic acid, Potassium, Magnesium, Iron, Zinc,	3/5
Manganese, Copper, Vanadium, Cobalt, Molybdenum, Selenium	
MUTAGENIC POTENTIAL In vitro	REVERSE MUTATION IN SALMONELLA THYPHIMURIUM
Ref. to document: HUM 008 Volume: Page: — Report date: 1 Oct. 1992 Number: 92/134-0	
Test cells: SALMONELLA THYPHII	MURIUM TA 1535
Test for induction of: base substitution and frame Metabolizing system: Aroclor 1254 induced rat li	
,	ion: 468.75, 937.5, 1875, 3750, 7500 µg/plate ion: 468.75, 937.5, 1875, 3750, 7500 µg/plate
Treatment and a) 48 h	ours, no recovery time
recovery time: b) 48 l	hours, no recovery time
	queous potassium-pyrophosphate potassium-pyrophosphate
Formulation of positive	
	un azide; 4 µg/plate nincanthracene; 4 µg/plate
Number of independent experiments: a) 2 (without metabolic activitation)	Number of replicate cultures: a) 3 plates per concentration
b) 2 (with metabolic activitation)	b) 3 plates per experiments
	a)
Number of cells analysed per culture :	b) —
Cytotoxic effects:	<u>.</u>
a)	
b) Genoloxic effects :	
a) The test substances did not induce increases in the s	number of revertant colonies
b) Similar to the control values at any dose-level, either	er in the absence or presence of S9 metabolism
Effects of the positive control:	•
a) 589 plate counts (exp.1) resp. 588 (exp.2); solvent b) 1486 plate counts (exp.1) resp. 559 (exp.2); solvent	control 14 (exp.1) resp. 14 (exp.2)
Additional data regarding methods and time schedu	le of the lest:
Test item was the lyophised form of the finisched prod To demonstrate mutagenic effect the concentration of	S9 fraction was increased up to 30 % and a 30 minutes
preincubation time was established in the second study	
Study conducted by the applicant : Yes	x No
If "no", indicate the name and address of the institu	ite that conducted the study:
Texicological Research Centre Ltd. Szabadságpus	· · · · · · · · · · · · · · · · · · ·
Study in compliance with GLP: x Yes	No Not required Page : 7

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Name of Company:		TA	BULATED		
HORIZON-MULTIPLAN Ltd.		STUI	Y REPORT		
Name of Finished Product:		ref.i	o III.D.110		
HUMET-R SYRUP					
Name of Active Ingredient :		Pag	e/Number		
Humic acid, Potassium, Magnesium, Iron,	7inc		15		
Manganese, Copper, Vanadium, Cobalt, M	olvhdenum.	ĺ		į	
Selenium	0., 000.12.1.1	l			
		DEVEDSE Y	IUTATION IN S	ALMONELLA	
MUTAGENIC POTENTIAL IN	ritro	THYPHIMU		APPLICATION.	
Ref. to document: HUM 008 Volume:	Page : -	to	Addendum N		
Report date: 1 Oct. 1992 Numl	ber: 92/134-0	07M	Study period (y	rears): 1992	
EATA/ONTO	T A TEXUDUS	MURIUM TA I	<11 ·		
1001000		shift point muts			
	induced rat li				
8 - 7					
Formulation of test substance			.5, 1875, 3750, 75		
and final concentration :	b) solut	юя: 408.75, 93 <i>1</i>	.5, 1875, 3750, 7;	on tradition	
Treatment and		urs, no recover			
recovery time:	b) 48 (nours, no recove	ry time		
Solvent and	2) 1%8	queous potassiu	m-pyrophosphate		
Final concentration:	b) 1% a	queous potassiu	m-pyrophosphate		
Formulation of positive					
Control and final	#) 4-nitr	o-o-ohenilenedi	amine; 4 µg/plate		
Concentration		ninoanthracene;			
Number of independent experiments :		No	mber of replicat	e cultures :	
a) 2 (without metabolic activitation)) 3 plates per co		
b) 2 (with metabolic activitation)) 3 plates per ex		
Number of cells analysed per culture:			¥)		
itante of community of personners		b)			
Cytotoxic effects:					
n)					
b)					
Genotoxic effects:					
a) The test substances did not induce inc b) Similar to the control values at any de	reases in the t	lumber of reven	an colonies	metabolism	
Effects of the nositive control:	DEC-JEACT CITIE	a in the Bosch	or presence or o	7 1174400113111	
a) 976 plate counts (exp. 1) resp. 625 (ex	n 71- eduant	control 13 (exp.	1) resp. 17 (exp.2	1	
h) 415 plate counts (exp.1) resp. 421 (exp.	(p.2): solvent	control 19 (exp	1) resp. 23 (exp.2	.)	
1					
Additional data regarding methods and -Test item was the lyophised form of the	i inne sched nood	ie of the test i	/I of dev remnant	content	
-To demonstrate mutagenic effect the cor	centration of	S9 fraction was	ncreased up to 30	% and a 30 minutes	
preincubation time was established in the	second study				
Study conducted by the applicant: 1	l Yes	Ixl No			
If "no", indicate the name and address	of the institu	te that conduc	led the study:		
Toxicological Research Centre Ltd.	Szabodságyus	zta Veszprém H	-8200 Hungary E	UROPE	
Study is compliance with GLI':	Ix Yes			Not required	
LOTHING IN COMMISSION TO THE COLOR OF	1-,			Page : 8	

Name of Company; TABULATED HORIZON-MULTIPLAN LIL STUDY REPORT Name of Finished Product: refito III.D.110 **HUMET-R SYRUP** Name of Active Ingredient : Page / Number 5/5 Humic acid, Potassium, Magnesium, Iron, Zinc, Manganese, Copper, Vanadium, Cobalt, Molybdenum, Selenium REVERSE MUTATION IN SALMONELLA MUTAGENIC POTENTIAL In vitro THYPHIMURIUM Ref. to document: HUM 008 Volume: Page: -Addendam No.:--Number: 92/134-007M Study period (years): 1992 Report date: 1 Oct. 1992 SALMONELLA THYPHIMURIUM TA 1537 Test cells : Test for induction of: base substitution and frameshift point mutation Aroclor 1254 induced rat liver S 9-mix Metabolizing system: a) solution: 468.75, 937.5, 1875, 3750, 7500 µg/plate Formulation of test substance b) solution: 468.75, 937.5, 1875, 3750, 7500 µg/plate and final concentration : Treatment and a) 42 hours, no recovery time b) 48 hours, no recovery time recovery time: a) 1% aqueous potassium-pyrophosphate Solvent and Final concentration: b) 1% aqueous potassium-pyrophosphate Formulation of positive a) 9-aminoscridine; 50 µg/plate Control and final b) 2-Aminoonthracene; 4 µg/plate Concentration Number of independent experiments: Number of replicate cultures: a) 3 plates per concentration a) 2 (without metabolic activitation) b) 2 (with metabolic activitation) b) 3 plates per experiments Number of cells analysed per culture: b) ---Cytotoxic effects: a) --b) ---Genotoxic effects: a) The test substances did not induce increases in the number of revertant colonies h) Similar to the control values at any dose-level, either in the absence or presence of S9 metabolism Effects of the positive control: a) 1958 plate counts (exp.1) resp. 253 (exp.2); solvent control 24 (exp.1) resp. 23 (exp.2) b) 1765 plate counts (exp.1) resp. 312 (exp.2); solvent control 24 (exp.1) resp. 29 (exp.2) Additional data regarding methods and time schedule of the test: -Test item was the lyophised form of the finisched product with a 78.5 g/l of dry remnant content -To demonstrate mutagenic effect the concentration of S9 fraction was increased up to 30 % and a 30 minutes preincubation time was established in the second study. Iz No Study conducted by the applicant: | | Yes If "no", indicate the name and address of the institute that conducted the study : Toxicological Research Centre Ltd. Szabadságnuszta Veszprém H-8200 Hungary EUROPF. | | Not required |x| Yes | | No Study in compliance with GLP:

Page: 9

Name of Company:	TABULATED			
	STUDY REPORT			
HORIZON-MULTIPLAN Ltd.	ref.to III.D.110			
Name of Finished Product:	16140 111.17.110			
HUMET-R SYRUP				
Name of Active Ingredient:	Page / Number			
Humic acid, Potassium, Magnesium, Iron, Zinc,				
Manganese, Copper, Vanadium, Cobalt, Molybdenum,				
Selenium	ANTI-CLASTOGENIC EFFECT OF HUMET_			
MUTAGENIC POTENTIAL In vitro	in human peripheral blood			
	LYMPHOCYTES			
Ref. to document : HUM 004 Volume : Page : -	- to Addendum No. : Study period (years): 1992			
Report date: 1992 Number:	Study period (Jen.s). 1222			
Test cells: Peripheral human lymphe	ocytes			
Test for induction of: Chromosomal aberration	•			
Metabolizing system: Non				
	ution: 10, 20, 100, 200 µl / ml culture			
Formulation of test substance a) soli And final concentration: b)	***************************************			
1000	hours incubation			
Treatment and	nours incubation			
2000423 22000	accondition to the second state of the second			
Solvent and a) media: 10 ml RPMI-	1640 + 0,8 ml blood + 0.2 ml Phytohemagglutinin M			
prepare cell division, after 48 hour colcemide 0.1 µg/n	nl to stop the cell division			
Final concentration: b)				
Formulation of positive				
Control and final a) N/	'A			
Concentration b)				
Number of independent experiments:	Number of replicate cultures:			
a) 2	a)			
b)	ь)			
Number of cells analysed per culture:	a) 600 in control, 200 in treated groups-			
	b)			
Genotoxic effects: Aberrations of chromosomes %	6			
	break dicentric chromosoma aberrant cell			
control 0 1	0 1			
Humet 10 µl/ml 0 0	0 0			
Humet 20 µl/ml 1 0	0 0			
Humet 100 μl/ml 1 0 Humet 200 μl/ml 0	U 1			
	0 0			
LODGEDITATIONS AID NOT TAVABLE Clastonenic office				
Concentrations did not reveal clastogenic effect				
Effects of the positive control: a) N/A				
Effects of the positive control: a) N/A b)	NI			
Effects of the positive control: a) N/A b) Additional data regarding methods and time schedu				
Effects of the positive control: a) N/A b) Additional data regarding methods and time schede Study conducted by the applicant: 1 Yes	[x] No			
Effects of the positive control: a) N/A b) Additional data regarding methods and time schede Study conducted by the applicant: Yes If "no", indicate the name and address of the insti	[x] No tute that conducted the study :			
Effects of the positive control: a) N/A b) Additional data regarding methods and time schede Study conducted by the applicant: Yes	[x] No tute that conducted the study: astitute 1138 Budapest Váci út 174. Hungary, EURO			

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